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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,250	07/24/2003	Raju Kucherlapati	Cell 4.4 CON	4128

1473 7590 03/22/2006

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 03/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,250	KUCHERLAPATI ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,14-16,25,27,34,35,40,50,52,54,57,60,67,68,70,72 and 75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1, 11, 14-16, 25, 27, 34-35, 40, 50, 52, 54, 57, 60, 67-68, 70, 72, and 75* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's preliminary amendment filed on 7/24/03, canceled claims 2-10, 12, 13, 17-24, 26, 28-33, 36-39, 41-49, 51, 53, 55, 56, 58, 59, 61-66, 69, 71, 73, 74, and 76-78. Thus, claims 1, 11, 14-16, 25, 27, 34-35, 40, 50, 52, 54, 57, 60, 67-68, 70, 72, and 75 are currently pending in the instant application.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, drawn to methods of producing a xenogeneic immunoglobulin by immunizing a transgenic non-human animal capable of producing a xenogeneic immunoglobulin, classified in class 800, subclass 6.

II. Claims 11, an immortalized non-human cell line comprising a xenogeneic immunoglobulin loci, classified in class 435, subclass 326.

III. Claim 14, drawn to methods of making a xenogeneic immunoglobulin by culturing an immortalized cell line, classified in class 435, subclass 70.21.

IV. Claims 15 and 70, drawn to a xenogeneic immunoglobulin, classified in class 530, subclass 387.1.

V. Claims 16, 34, 68, 72, and 75, drawn to a genetically modified non-human mammal whose genome is heterozygous or homozygous for a modification that results in the inability of a locus to produce endogenous immunoglobulin **heavy** chains, classified in class 800, subclass 13.

VI. Claims 16, 34, 68, 72, and 75, drawn to a genetically modified non-human mammal whose genome is heterozygous or homozygous for a modification that results in the inability of a locus to produce endogenous immunoglobulin **light** chains, and methods of making the homozygous mammal by breeding, classified in class 800, subclass 13.

VII. Claims 16, 25, 34, 68, 72, and 75, drawn to a genetically modified non-human mammal whose genome is heterozygous or homozygous for a modification that results in the inability of a locus to produce endogenous immunoglobulin **heavy and light** chains, and methods of making the homozygous mammal by breeding, classified in class 800, subclass 13.

VIII. Claims 16, 34, 68, 72, and 75, drawn to a genetically modified non-human mammal whose genome is heterozygous or homozygous for a modification that results in the inability of a locus to produce endogenous immunoglobulin **heavy and light** chains, and hemizygous or homozygous for the ability to produce xenogeneic immunoglobulin **heavy** chains, and methods of making the homozygous mammal by breeding, classified in class 800, subclass 13.

IX. Claims 16, 34, 68, 72, and 75, drawn to a genetically modified non-human mammal whose genome is heterozygous or homozygous for a modification that results in the inability of a locus to produce endogenous immunoglobulin **heavy and light** chains, and hemizygous or homozygous for the ability to produce xenogeneic immunoglobulin **light** chains, and methods of making the homozygous mammal by breeding, classified in class 800, subclass 13.

X. Claims 16, 34, 68, 72, and 75, drawn to a genetically modified non-human mammal whose genome is heterozygous or homozygous for a modification that results in the inability of a locus to produce endogenous immunoglobulin **heavy and light** chains, and hemizygous or homozygous for the ability to produce xenogeneic immunoglobulin **light** chains, and methods of making the homozygous mammal by breeding, classified in class 800, subclass 13.

XI. Claims 16, 34, 68, 72, and 75, drawn to a genetically modified non-human mammal whose genome is heterozygous or homozygous for a modification that results in the inability of a locus to produce endogenous immunoglobulin **heavy and light** chains, and hemizygous or homozygous for the ability to produce xenogeneic immunoglobulin **heavy and light** chains, and methods of making the homozygous mammal by breeding, classified in class 800, subclass 13.

XII. Claims 16, 34, 68, 72, and 75, drawn to a genetically modified non-human mammal whose genome is heterozygous or homozygous for a modification that results in the inability of a locus to produce endogenous immunoglobulin **heavy** chains, and hemizygous or homozygous for the ability to produce xenogeneic immunoglobulin **heavy and light** chains, and methods of making the homozygous mammal by breeding, classified in class 800, subclass 13.

XIII. Claims 16, 34, 68, 72, and 75, drawn to a genetically modified non-human mammal whose genome is heterozygous or homozygous for a modification that results in the inability of a locus to produce endogenous immunoglobulin **light** chains, and hemizygous or homozygous for the ability to produce xenogeneic

immunoglobulin **heavy and light** chains, and methods of making the homozygous mammal by breeding, classified in class 800, subclass 13.

XIV. Claims 27 and 60, drawn to a method for producing a modified non-human animal having a xenogeneic DNA segment, or a method of producing a murine embryonic stem cell having a large xenogeneic DNA genomic fragment, classified in classes 800 and 435, subclasses 21 and 455 respectively.

XV. Claims 34 and 68, drawn to a modified animal having a xenogeneic DNA segment which is not immunoglobulin DNA, classified in class 800, subclass 13.

XVI. Claims 40, 50, and 54, drawn to an embryonic stem cell comprising a genome comprising a lesion in the endogenous **heavy** chain loci, classified in class 435, 325.

XVII. Claims 40, 52, and 54, drawn to an embryonic stem cell comprising a genome comprising a lesions in the endogenous **light** chain loci, classified in class 435, 325.

XVIII. Claim 40, drawn to an embryonic stem cell comprising a genome comprising a lesions in the endogenous **light chain and heavy chain** loci, classified in class 435, 325.

XIX. Claims 57 and 67, drawn to an embryonic stem cell comprising at least 100 kb of xenogeneic DNA, classified in class 435, 325.

Claims 34 and 68 link inventions V-XIII, and XV. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claims, claims 34 and 68. Upon

the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions **shall** be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with **37 CFR 1.104** Claims that require all the limitations of an allowable linking claim will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by **37 CFR 1.116**; amendments submitted after allowance are governed by **37 CFR 1.312**.

The inventions are distinct, each from the other because of the following reasons:

1) Invention I is patentably distinct from inventions II and III in that the immortalized cell line is not required for the methods of invention I. Further the methods of inventions I and III are substantially different in starting materials and techniques as invention I utilizes a genetically modified mammal and requires in vivo immunization whereas the method of III is an in vitro method of culturing an immortalized cell. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.
2) Inventions I and IV are related as method of making a product and product made. The inventions are distinct if **either** or both of the following can be shown: (1) that the process as claimed can be used to make another materially different product or (2) that the product as claimed can be made by another materially different process (**MPEP § 806.05(f)**). In the instant case, the product can be made by several different methods,

such as the isolation of the immunoglobulin from cultured immortalized cell lines rather than from a genetically modified mammal.

3) Inventions I and Inventions V-X, and XII-XIII are patentably distinct in that the methods of invention I do not use the mammals of inventions V-X and XII-XIII, and in that the mammals can be used for substantially different purposes, such as the use of the mammals to produce B cells for hybridoma production, or the use of the mammals to study infection in the absence of endogenous antibody. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.

4) Invention I and Invention XI are related as product and process of use. The inventions can be shown to be distinct if **either** or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See **MPEP § 806.05(h)**. In the instant case, the mammals of invention XI can be used in materially different processes, such as the use of the mammals to produce B cells for hybridoma production.

5) Invention I and III, and Invention XIV are patentably distinct in that the methods are unrelated. None of these methods use the same reagents, techniques, or conditions. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.

6) Invention I and XV are related in part as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for

using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See **MPEP § 806.05(h)**. In the instant case, the mammals of invention XV can be used in materially different processes, such as the use of the mammals to produce proteins which are not immunoglobulins, further the methods of invention I do not required the mammals of invention XV as they can be practiced with mammal that do not contain 100kb of xenogeneic genomic DNA, but rather contain an immunoglobulin minilocus or DNA encoding rearranged non-genomic xenogeneic DNA.

7) Inventions I and XVI-XIX are patentably distinct in that the embryonic stem cells of inventions XVI-XIX are not required or useful in the methods of invention I. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.

8) Invention II and Invention III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See **MPEP § 806.05(h)**. In the instant case, the immortalized cells can be used for materially different process such as the use of the cells to clone the xenogeneic immunoglobulin, or the use of the cells for transplantation into a mammal.

9) Inventions II and IV are patentably distinct in that the immortalized cell line is substantially different from an immunoglobulin in structural, chemical, and biological

properties, is made using different techniques, and can be used for materially different purposes. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.

10) Inventions III and IV are related as method of making a product and product made. The inventions are distinct if **either** or both of the following can be shown: (1) that the process as claimed can be used to make another materially different product or (2) that the product as claimed can be made by another materially different process (**MPEP § 806.05(f)**). In the instant case, the product can be made by several different methods, such as the isolation of the immunoglobulin from a genetically modified mammal.

11) Inventions II -IV are patentably distinct from inventions V-XIX. The methods of invention III do not use or require any of the products or methods of inventions V-IX. Further, neither the immortalized cell line of invention II nor the immunoglobulin of invention IV is used in any of the methods of inventions V-XIV, and both are materially different in structural, chemical, and biological properties from the mammals and embryonic stem cells of inventions V-XIII and XV-XIX. Finally, the immortalized cells can be made by transfection of various genetic constructs in vitro and do not require the genetically modified mammals of any of invention V-XIII. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.

12) Inventions V-XIII are patentably distinct in that the specific combination of genetic modifications for each of the mammals of inventions V-XIII render each mammal materially different in structural, chemical, and biological properties. Further, each

mammal is made using different reagents. Specifically, the endogenous heavy chain locus is a separate and distinct genetic locus from the endogenous light chain locus and thus modifying each locus requires distinct genetic constructs that are not interchangeable. Likewise a xenogeneic DNA encoding a light chain is materially different from a xenogeneic DNA encoding a heavy chain. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.

13) Inventions V-XIII and Invention XIV are related in part as method of making a product and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another materially different product or (2) that the product as claimed can be made by another materially different process (**MPEP § 806.05(f)**). In the instant case, the product can be made in the absence of the 100 kb of xenogeneic DNA required for the methods of invention XIV. The products of inventions V-XIII can be made using smaller fragments of xenogeneic genomic immunoglobulin DNA or non-genomic rearranged immunoglobulin heavy and/or light chain DNA. Further, the methods can be used to make materially different products, such as the use of the methods to produce mammals with non-immunoglobulin xenogeneic genomic DNA.

14) Inventions V-XIII and Invention XV are patentably distinct in that the mammals of inventions V-XIII have genetic modifications to the immunoglobulin loci and further may comprise xenogeneic immunoglobulin DNA, either genomic or non-genomic, which causes these mammals to be structurally, chemically, and biologically distinct from the

mammals of invention XV which comprise non-immunoglobulin xenogeneic genomic DNA. Further, the mammals of inventions V-XIII are made using different reagents and are used for different purposes than the mammals of invention XV. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.

15) Inventions V-XIII, XV and Inventions XVI-XIX are patentably distinct in that the mammals of inventions V-XIII,XV and the embryonic stem cells of XVI-XIX are distinct products with materially different chemical, structural, and biological properties, are made using different techniques and reagents and are used for materially different purposes. Further, the embryonic stem cells are not required for making the mammals as the mammals can be made using microinjection. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.

16) Invention XIV and Invention XV are related in part as method of making a product and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another materially different product or (2) that the product as claimed can be made by another materially different process (**MPEP § 806.05(f)**). In the instant case, the product can be made using a materially different process with does not utilize spheroplast fusion, such as the microinjection of the DNA into an embryo.

17) Inventions XIV and Inventions XVI-XVIII are patentably distinct in that the methods of invention XIV does not produce the embryonic stem cells of inventions XVI-XVIII and

in that the embryonic stem cells can be used in materially different methods such as methods of differentiating cells in culture. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.

18) Inventions XIV and Invention XIX are related in part as method of making a product and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another materially different product or (2) that the product as claimed can be made by another materially different process (**MPEP § 806.05(f)**). In the instant case, the product can be made using a materially different process with does not utilize spheroplast fusion, such as the microinjection of the DNA into the embryonic stem cell.

19) Inventions XVI-XIX are patentably distinct in that each of the embryonic stem cell products has different genetic modifications that render the cells structurally, chemically, and biologically different. As such, the search for each is not co-extensive and it would place an undue burden on the examiner to search and examine all the inventions together.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, different classification, and different search requirements, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species and/or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology

center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER